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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/532,001	03/21/2000	Thomas John Goodwin	MSC-22859-2-CU	7201

24957

7590

09/23/2002

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EXAMINER

LACOURCIERE, KAREN A

ART UNIT

PAPER NUMBER

1635

DATE MAILED: 09/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/532,001	GOODWIN ET AL.	
	Examiner	Art Unit	
	Karen Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5-10 and 27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-10 and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 July 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>7</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Drawings***

The corrected or substitute drawings were received on 07-09-2002. These drawings are acceptable.

Sequence Listing

The submission of a statement in support of request for transfer of the Computer Readable Copy of the Sequence Listing in parent Serial No. 09/056,363 in accordance with 37 CFR 1.821(e) is acknowledged. The CRF has been transferred.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 13, submitted as part of the amendment filed Jan 22, 2002 has been renumbered as claim 27.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-10 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and claims dependent on claim 1, are indefinite due to the recitation "directed against a nucleotide sequence encoding a shear stress response element". The term "directed against" has not been defined in the specification, nor is there an art accepted meaning for this phrase and the skilled artisan would not recognize what relationship the nucleotide sequence and the oligonucleotide sequence have. It is unclear what the term "directed against" would encompass; therefore the metes and bounds of the claimed methods are unclear.

Claim 6 is indefinite because it is dependent upon claim 4, which has been canceled. One skilled in the art would not know what methods are encompassed in claim 6, because it is unclear what limitations are provided by "claim 4", which is no longer pending.

Claim 6 recites the limitation "said cell" in line one of the claim. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 10 has been amended to include the limitation, "wherein the concentration of said oligonucleotide is from about 10 nM to about 10 mM". Support cannot be found in the originally filed claims or specification for the limitations "10 nM" and "10mM" and is considered to be new matter.

Claims 1-3, 5, 7-10, and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-3, 5, 7-10 and 27 are drawn to methods of inducing expression of a target gene in a cell in culture by contacting the cell with a transcription factor decoy directed against a shear stress response element.

The specification provides the structure of one transcription factor decoy (SEQ ID NO: 1, figure 4) targeted to a shear stress response element. The specification also discloses two subsequences, 3'-GAGACC-5' and its complement, 3'-GGTCTC-5', which are preferred embodiments of the shear stress response element. The specification does not provide the sequence of transcriptional factor decoys that up regulate the expression of megalin, cubulin, erythropoietin or 1- α -hydroxylase. Claims 1-3, 5, 7-10 and 27 encompass SSRE decoy oligonucleotides in any cell type or organism and SSRE sequences which regulate the expression of a wide variety of genes. Multiple SSRE elements exist, not all of which comprise the one structural element described in

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the specification (the sequence 3'-GAGACC-5', or its complement). For example, Ando et al. (Jpn Heart J., Vol. 37, No. 1, Jan. 1996, p19-32) indicate that numerous SSRE appear to exist and note that genes up regulated by shear stress do not require a 3'-GAGACC-5' sequence (see for example, Ando et al., page 27, second paragraph). Additionally, the claims encompass decoy oligonucleotides comprising 3'-GAGACC-5' or 3'-GGTCTC-5' and further comprise flanking sequences which are specific to particular gene targets, which have not been described in the specification or the prior art. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim, because the genus is very broad and highly variant with regard to structure (i.e. nucleotide sequence). The one decoy sequence, SEQ ID NO:1, and the subsequence 3'-GAGACC-5' and its complement, 3'-GGTCTC-5', would not provide sufficient written description to determine the structure, i.e. nucleotide sequence, or the full genus of sequences encompassed in the claims. For example, the specification has not described any other SSRE decoy sequence, nor has it described the structure, i.e. nucleotide sequence, for the flanking sequences that would be required for all decoy oligonucleotides comprising 3'-GAGACC-5' and its complement, 3'-GGTCTC-5', nor has the specification described the sequences for SSRE's that regulate expression of megalin, cubulin, erythropoietin or 1- α -hydroxylase.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the

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'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Therefore, only SEQ ID NO: 1, but not the full breadth of the claim, meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 7, 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Khachigian et al. (J. Clin. Invest. V. 96, Aug 1995, p 1169-1175, cited in prior Office action).

Claims 1, 5, 7, 8 and 10 are drawn to methods of inducing expression of at least one gene in a cultured cell wherein the cell is cultured, contacted with a transcription factor decoy oligonucleotide sequence directed against a shear stress response element and the expression of the gene is determined. Further limitations include the cell is endothelial, the cell is grown in two dimensional culture, the shear stress

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response element is GGTCTC and the oligonucleotide sequence is between 10 nM and 10 mM.

Khachigian et al. disclose culturing Bovine endothelial cells in two dimensional culture, transforming with an oligonucleotide comprising a shear stress response element sequence comprising the sequence GGTCTC, which the specification indicates is a shear stress response element sequence, inducing the expression of CAT gene, and measuring the expression of said CAT gene. Therefore, Khachigian et al. anticipates claims 1, 5, 7, 8 and 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 7, 8, 10 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dzau et al. (WO 95/11687) in view of Khachigian et al. (J. Clin. Invest., V. 96, Aug 1995, cited in prior Office action) and Goodwin et al. (reference 1 on PTO form 1449, filed Jan 30, 2002, J. Cell Biochem. 51:301-311, 1993).

Dzau et al. teach using transcription factor oligonucleotide decoys to up regulate the expression of genes and specifically teach using decoys for the regulation of shear stress response elements (see for example p 4) in cells ex vivo (in culture), including endothelial cells in graft transplant tissues. Dzau et al. teach their decoys with phosphorothioate modifications throughout the oligonucleotide and teach using these oligonucleotides within the range of 10 nM and 10 mM (see for example, p 7, last paragraph).

Dzau et al. do not teach the sequence of shear stress response element decoys. Dzau et al. do not teach growing cells in rotating wall vessels.

Khachigian et al. teach the sequence of a shear stress response element active in endothelial cells, which includes the sequence GGTCTC.

Goodwin et al. teach growing tissues in rotating wall vesicles as a constructive tool for the growth of three-dimensional tissues.

At the time the instant invention was made, it would have been obvious to one of ordinary skill in the art to up regulate the expression of a gene in endothelial cells in culture using an oligonucleotide decoy comprising an SSRE sequence, as taught by Dzau et al., using the SSRE sequence taught by Khachigian et al. because Dzau et al. teach it is useful to use such decoys in vascular tissues ex vivo in vascular transplant

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cells and Khachigian et al. teach that their SSRE is active for regulating gene expression in endothelial cells in vascular tissue. One of ordinary skill in the art would have been motivated to use the SSRE sequence taught by Khachigian et al. because Dzau et al. teach that the decoy sequences used in their methods are designed based on the sequence of the particular transcription factor targeted and Khachigian et al. teach that their sequence is an SSRE sequence which regulates factors involved in altered vascular reactivity and structural remodeling that typically occurs in hypertensive and atherosclerotic vascular disease. It further would have been obvious to grow such cells in a rotating wall vessel, as taught by Goodwin et al., because rotating wall vessels were known to provide the proper environment for growing three dimensional tissues. One of ordinary skill in the art would have been motivated to grow the cultured cells in rotating wall vessels in order to grow the tissues in an environment to support proper tissue cell growth for use in ex vivo transplant tissue methods, as suggested by ^{Dzau} ~~dza~~ et al. KAL 09-19-02

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

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308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
September 19, 2002



KAREN LACOURCIERE
PATENT EXAMINER